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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,463	03/21/2005	Chantal Guillemette	6013-118US	7564

20988 7590 04/26/2007

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,463	GUILLEMETTE, CHANTAL	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,8-11,13-15 and 17-32* is/are pending in the application.

4a) Of the above claim(s) *18-24 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8-11,13-15,17, and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/28/2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed April 12, 2007. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made FINAL.

Claims 1-2, 5, 8-11, 13-15, and 17-32 and are currently pending. Claims 1, 5, 8, 13, 17, 18-20, and 22-23 have been amended. Claims 30-32 are newly presented. Claims 18-29 and 31 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Therefore Claims 1-2, 5, 8-11, 13-15, 17, 30 and 32 will be addressed herein.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a new ground of rejection necessitated by applicants amendments to claim 1 which recite "A method for determining the predisposition of a human individual to a variation in glucuronidation activity of a biologically active compound that is that is metabolized through glucuronidation, said method comprising determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of exon 1 or the

promoter of UGT1A9". The new ground of rejection also includes newly presented claims 30 and 32.

Claims 1-2, 5, 8-11, 13-15, 17, 30, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn broadly to encompass a method for determining the predisposition of a human individual to a variation in glucuronidation activity of a biologically active compound that is metabolized through glucuronidation, said method comprising determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of exon 1 or the promoter of UGT1A9. Thus the claims are drawn to detecting any sequence variation in exon 1 or the promoter of UGT1A9. The claims do not define the nucleotide variation in terms of particular structure or function.

The specification at page 20 teaches 2 missense mutations in the UGT1A9 gene that result in amino acid substitutions in the UGT1A9 protein, namely the C3Y and the M33T amino acid substitutions. The mutations that result in the C3Y and the M33T substitutions occur in exon 1. The specification further teaches on page 24 ten polymorphic mutations within the UGT1A9 promoter region. The specification also teaches several haplotypes of the UGT1A9 which are presented in Table 11. It is noted that the specification teaches mutations present only in exon 1 and the promoter of the UGT1A9 gene. While methods which specifically detect the C3Y and M33T

mutations in exon 1 and the 10 specific mutations recited on page 24 in the promoter region of UGT1A9 meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus required by the claims of any variation in the UGT1A9 gene.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that 'An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, 12 members of the genus of UGT1A9

nucleotide variations have been identified. No additional nucleotide variations have been disclosed in the specification or prior art. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided for any of allelic variants or mutant UGT1A9 nucleic acids. Yet, the claims as written are inclusive of a potentially large genus of mutations in the UGT1A9 gene. While one could contemplate a nucleotide substitution, deletion or addition at each and every position in the UGT1A9 gene, such nucleotide variations are not considered to be equivalent to specific nucleotide variations associated with causing a physiological reaction to a biologically active compound. Rather, mutations in the UGT1A9 gene that do cause physiological reactions to biologically active compounds represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. Conception of the claimed invention cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of potential methods for isolating additional nucleotide variations. As stated in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. LTD*, 25 USPQ2d 1016, one cannot describe what one has not conceived.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 'Written Description" Requirement, Federal Register; Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Response to Arguments

3. In the response filed March 28, 2007, Applicants amended claim 1 to overcome the written description rejection. Specifically the claims now recite "determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of exon 1 or the promoter of UGT1A9". The amendments have been fully considered but are not sufficient to overcome the written description rejection. In the instant case, the claims still lack written description because the claim language encompasses the detection of any variation in the nucleotide sequence of exon 1 or the promoter of the UGT1A9 gene. The claims do not define the nucleotide variation of in terms of particular structure or function. Exon 1 and the promoter region of the UGT1A9 gene are both expected to contain numerous polymorphisms, however the specification only teaches 2 mutations in exon 1 and 10 mutations in the promoter of the UGT1A9 gene. For these reasons, Applicants have not provided sufficient evidence that they were in possession of any nucleotide variation in the nucleotide sequence of exon 1 or the promoter of UGT1A9.

4. The following is a new ground of rejection necessitated by applicants amendments to claim 1 which recite "A method for determining the predisposition of a human individual to a variation in glucuronidation activity of a biologically active compound that is that is metabolized through glucuronidation, said method comprising determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of exon 1 or the promoter of UGT1A9". The new ground of rejection also includes newly presented claims 30 and 32.

Claims 1-2, 5, 8-11, 13-15, 17, 30, and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a human that has a higher glucuronidation rate with SN-38 comprising obtaining a DNA sample from said human and determining the presence of the T(-275)A variant in the promoter region of the UGT1A9, wherein the presence of A at position –275 is indicative that said human will have a higher glucuronidation rate with SN-38, does not reasonably provide enablement for a method for determining the predisposition of a human individual to a variation in glucuronidation activity of a biologically active compound that is metabolized through glucuronidation, said method comprising determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of exon 1 or the promoter of UGT1A9 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the

nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claim 1 is drawn broadly to a method for determining the predisposition of a human individual to a variation in glucuronidation activity of a biologically active compound that is metabolized through glucuronidation, said method comprising determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of exon 1 or the promoter of UGT1A9 gene. This claim reads on any type of sample, any type of variation in glucuronidation activity, any biologically active compound that is metabolized through glucuronidation, and any polymorphic or haplotypic variation in exon 1 or the promoter of UGT1A9.

Nature of the Invention

The claims are drawn to a method for determining the predisposition of a human individual to a variation in glucuronidation activity of a biologically active compound that is metabolized through glucuronidation. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches on page 1 that the UDP-glucuronosyltransferase enzymes are a set of enzymes that increase the polarity of xenobiotics, drugs, and endogenous compounds to facilitate their excretion from the body. Any perturbation in the glucuronidation pathway has the potential to modify the elimination, the detoxification or the pharmacokinetic parameters of a given drug, and consequently drug clearance. Thus human genetic variation leading to differences in the glucuronidation rates could influence the activity of drugs and other chemicals. The specification on page 16 further teaches that DNA samples from 201 Caucasian subjects were used to genotype the UGT1A9 gene. The specification does not teach any other type of samples being used. The specification teaches on page 20, two missense mutations in the UGT1A9 gene that result in amino acid substitutions in the UGT1A9 protein, namely the C3Y and the M33T amino acid substitutions. The mutations that result in the C3Y and the M33T substitutions occur in exon 1. The specification further teaches on page 24 ten polymorphic mutations within the UGT1A9 promoter region. The specification also teaches UGT1A9 promoter haplotypes (See Table 11). It is noted that Table 11 teaches the frequencies of these haplotypes in the populations, however the specification does not provide any information on the percentage of linkage disequilibrium between these SNPs. The specification does not teach any additional mutations in exon 1 or the promoter region of the UGT1A9 gene. In addition to genotyping, the effect of UGT1A9 polymorphic variations on live microsomes glucuronidation was determined. The specification states on page 25 that there was a positive correlation between the presence of the –275 mutated alleles and

higher glucuronidation rate with SN-38 (See Fig 12). It is noted that Fig 12 shows that carriers of the –275 allele have a higher glucuronidation rate than non-carriers however there is sufficient overlap on the graph and it cannot be determined if these results are significant. Additionally the specification teaches that SN-38 is the pharmacologically active metabolite of the anticancer drug irinotecan which undergoes extensive glucuronidation in humans to form SN-38-G. The specification does not teach an association between the –275 mutated alleles and any other biologically active compound. Further the specification does not teach an association between the –275 mutated alleles and any other physiological reaction besides a higher glucuronidation rate.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying novel variants in UGT1A9 gene which are associated with higher glucuronidation rates with SN-38 is highly unpredictable. Knowledge of the sequence of the wild type UGT1A9 gene does not allow one to immediately envision additional mutations in exon 1 or the promoter region of the UGT1A9 gene that are associated with higher glucuronidation rates with SN-38. The UGT1A9 gene is expected to contain numerous polymorphisms. This finding is supported by the teachings in the post filing date art of Carlini et al (Clinical Cancer Research 2005) teaches several additional polymorphisms identified in the coding region, the promoter region, and non-coding regions of UGT1A9 (see page 1228). However, the specification does not teach a predictable means for identifying additional variations associated with a higher glucuronidation rate with SN-38. Without extensive information regarding the structure-

function relationship between the UGT1A9 gene and glucuronidation, it is highly unpredictable as to what would be the identity of additional mutant, allelic, or splice variants which would be associated with a higher glucuronidation rate with SN-38.

It is also unpredictable as to whether the results obtained with SN-38 can be extrapolated to other biologically active compounds that are metabolized through glucuronidation. SN-38 is the pharmacologically active metabolite of the anticancer drug irinotecan. The teachings in the specification are limited to an association between the –275 mutation and a higher glucuronidation rate with SN-38. There are no teachings in the specification regarding the –275 mutation and the glucuronidation rate of other drugs, particularly anticancer drugs. Accordingly, it is unpredictable as to whether the presently claimed method can be used to determine the predisposition of any individual to any biologically active compound.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches that the –275 mutation of the UGT1A9 gene is associated with higher glucuronidation rates with SN-38. To identify additional variants of the UGT1A9 gene which are associated with higher glucuronidation rates with SN-38 and other biologically active compounds would require extensive experimentation. For example, such experimentation may involve sequencing the UGT1A9 gene of individuals and then exposing them to SN-38 or other biologically active compounds and then determining the glucuronidation rates. The results of performing such methodology is highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying

additional variants of the UGT1A9 gene which are associated with higher glucuronidation rates.

Working Examples:

Again the specification teaches the –275 mutation of the UGT1A9 gene is associated with higher glucuronidation rates with SN-38. There are no specific examples provided in the specification in which the –275 mutated alleles were associated with a higher glucuronidation rates with any other biologically active compound. Further there are no specific examples provided in the specification in which the –275 mutated alleles were associated with any other type of physiological reaction with SN-38. Additionally there are no specific examples in which non-human organisms were used.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of

one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims are not enabled because the specification does not teach a representative number of variants of the UGT1A9 gene which are associated with a higher glucuronidation rate with SN-38. The specification does not teach any additional physiological reactions associated with this mutation or that this mutation is associated with a higher glucuronidation rate with any other biologically active compounds. Additionally, the disclosure of a single organism (i.e. humans) is not representative of the broadly claimed genus of any individual. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to Arguments

5. In the response filed March 28, 2007, Applicants amended claim 1 to overcome the enablement rejection. Specifically the claims now recite "a method for determining the predisposition of a human individual to a variation in glucuronidation activity of a biologically active compound that is metabolized through glucuronidation, said method comprising determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of exon 1 or the promoter of UGT1A9...". The amendments have been fully considered but are not sufficient to overcome the enablement rejection. In

the instant case, the claims still lack enablement because the claim language encompasses using any type of sample, detecting any variation in glucuronidation activity, any biologically active compound, and any variant in exon 1 or the promoter of UGT1A9. First it is noted that the applicants have not addressed the issue pertaining to the type of sample that is used. The specification on page 16 teaches that DNA samples of 201 Caucasian subjects were used to identify UGT1A9 variants. However the claims encompass using any type of sample when really they are only enabled for using DNA samples. It is also noted that the claims encompass detecting any type of variation in glucuronidation activity which causes a physiological reaction selected from an adverse reaction, a side effect, a variation in response to therapy, and a modified ability. The specification teaches on page 25 that there is a positive correlation between the presence of the T (-275)A variant (which is the variant that was elected in the response filed 11/3/2006) and a higher glucuronidation rate with SN-38. However the claims encompass any type of variation in glucuronidation activity when really they are only enabled for "a higher glucuronidation rate". Further it is unclear what type of physiological reaction would be caused by "a higher glucuronidation rate". The claims also encompass a large number of compounds that are metabolized through glucuronidation. The specification on page 24 teaches that a correlation study was done to determine if a correlation exists between the mutation at –275 and SN-38, mycophenolic acid, and 4-hydroxyestrone glucuronide formation. The results presented on page 25 show a positive correlation between the presence of the T(-275)A variant and a higher glucuronidation rate with SN-38. However the claims encompass any

compounds that are metabolized through glucuronidation when really they are only enabled for the compound SN-38. Finally it is also noted that the claims encompass detecting any variant in exon 1 or the promoter of UGT1A9. In the instant case the Applicants have elected to have the T(–275)A searched. This variant is present in the promoter region of the UGT1A9 gene. As mentioned above page 25 shows a positive correlation between the presence of the T(-275)A variant and a higher glucuronidation rate with SN-38. However the claims encompass detecting any variant in exon 1 or the promoter of UGT1A9 when really they are only enabled for detecting the T(-125)A variant in the promoter region of the UGT1A9 gene. For these reasons the enablement rejections is maintained.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

DIANA JOHANNSEN
PRIMARY EXAMINER